CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75-374

Bioequivalence Review(s)

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 75-374 APPLICANT: Altana Inc.

DRUG PRODUCT: Diflorasone diacetate 0.05% ointment

The Division of Bioequivalence has completed its review and has no further questions at this time.

Please note that the bioequivalency comments provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these reviews may result in the need for additional bioequivalency information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

Dale P. Conner

Dale P. Conner, Pharm.D.
Director Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

Diflorasone diacetate
0.05% ointment
NDA #75-374
Reviewer: J. Lee
75374S.898

Altana Inc.
Melville, NY
Submission date:
May 1, 1998
August 11, 1998

Review of a pilot dose-response study and a pharmacodynamic bioequivalence study

The following studies follow the guidance issued by OGD on topical dermatological corticosteroids.

Pilot Dose-response Study:

Objective:

To demonstrate dose response relationship of Psorcon® 0.05% ointment (Pharmacia & Upjohn) and determine the population ED_{50} for its vasoconstrictor response.

The pilot study (#9628201D) was conducted at Novum, Inc. in Pittsburgh, PA, under the supervision of Adelaida M. Miro, M.D., Principal Investigator.

Fifteen pre-screened, asymptomatic, female volunteers between the ages of 20-40 years and within 15% of ideal body weight for her height and frame were enrolled in the study.

All selected volunteers were in good health as determined by a medical history and physical examination; subjects were also evaluated for a positive vasoconstrictor response to the RLD.

The study was designed as a single period study. The treatment was:

Psorcon®
0.05% ointment, batch #09100
Pharmacia & Upjohn
expiry date: November, 1998

Eight circular (- diameter) application sites were designated on the flexor surface of each forearm. Seven skins sites on each arm were randomly assigned to a dose duration of 10, 20, 30, 45 minutes, 1, 1.5 or 3 hours. One untreated site on each arm was used as a control. (see pp. 1176-7, vol 1.4) All dose durations were applied staggered and removed at the same time point (0.0 hour).

Baseline chromameter readings were recorded one hour prior to the 3-hour dose application. All designated sites were treated with 10 mcl of the test formulation. The administered formulation

was dispersed over the entire spot using the conical end of a 1.5 mL polypropylene microcentrifuge tube. Skin blanching was evaluated using a chromameter at 0, 2, 4, 6, 8, 10, 12, 20 and 24 hours after drug removal.

Method Validation:

The sponsor has documented precision of drug application and reproducibility of chromameter readings. Chromameter reproducibility was based on multiple readings (5 per site) by two readers at 4 untreated skin sites on each arm of at least 4 different subjects. Reproducibility of drug application was determined by administration of 10 mcl doses. Precision (%CV) demonstrating reproducibility of chromameter readings (within-site) was ~5.8%. Between-site variability was ~12.5%.

Data Analysis:

The chromameter data were normalized for baseline values and changes in the color of the untreated skin as recommended in the guidance. AUEC's were calculated for 0-24 hours after drug removal using the trapezoidal rule. The pooled AUEC data as a function of the dose duration were fitted to the simple E_{max} model using P-PHARM (Simed, France), to determine the population ED_{50}.

Results:

Based on nonlinear mixed effect modeling, values of pharmacodynamic parameters calculated by the sponsor and the reviewer presented below:

Chromameter Method

Parameter	Sponsor (A)	Reviewer (B)	A/B
ED_{50} (min)	29.54	30.64	0.96
E_{max}(a scale units*min)	-58.22	-62.02	0.94

These data are indicative of a population ED_{50} value of approximately 30 minutes. Based on the pilot study results the sponsor used a dose duration of 30 minutes in the pivotal bioequivalence study.

Pivotal Bioequivalence Study:

Objective:

To determine the bioequivalence of two diflorasone diacetate 0.05% ointments (Altana product vs Psorcon®) using a vasoconstrictor method.

The pivotal study employed the same principal investigator and study site as the pilot study.

Fifty-nine female subjects between the ages of 18-47 years were pre-screened for a vasoconstrictor response to Psorcon® 0.05% ointment.

The study (#9728203) was a randomized, one-period study. Treatments consisted of the following:

A. Diflorasone diacetate
0.05% ointment, batch #9368
Altana Inc.
mnfg date: 3/97

B. Psorcon®
0.05% ointment, batch #09100
Pharmacia & Upjohn
expiry date: 11/98

The subjects were entered into the study as 3 dosing groups:

Group I - subj. #1-19 (dosed on 12/6/97)
Group II - subj. #20-34 (dosed on 12/13/97)
Group III - subj. #35-59 (dosed on 12/20/97)

A 10 mcl amount of each ointment was applied 8 sites on the flexor surface of each subject's arms and left in place for 30 minutes (duration time on the linear, non-saturation portion of the dose-response curve determined in the pilot study) according to the randomization schedule on pp. 341-2, vol. 1.2. Psorcon® ointment was also applied to two additional sites on each forearm for durations of 15 minutes (D_1) and 60 minutes (D_2), respectively. Two untreated sites were designated on each forearm as chromameter reference sites.

Assessment of vasoconstriction was the same as that used in the pilot study.

No treatment related adverse reactions were reported.

Data Analysis:

Chromameter data were transformed and AUEC's were calculated as mentioned in the pilot study review. The ratio of mean $AUEC_{0\text{-}24}$ value (average of left and right arm values) for D_2/D_1 was calculated for each subject. Subjects whose D_2/D_1 ratios were ≥ 1.25 were considered to be "evaluable subjects" and included in the statistical analyses. The $AUEC_{0\text{-}24}$ data for evaluable subjects were used to calculate the 90% confidence intervals.

Visual readings were also taken, but were not evaluated per Guidance.

Results:

Among the 59 subjects who entered the study, there were 41 evaluable subjects (# 1-2, 5, 10-16, 18-20, 24, 26, 28-9, 32-3, 36-9, 42-59) for the statistical analyses per Guidance.

AUEC

Test	Reference	T/R
-26.36	-27.06	0.9741

The 90% shortest confidence interval for AUEC is: [89; 107].

In-vitro release data is not required per Guidance.

Recommendation:

1. The pilot dose-response and pivotal pharmacodynamic bioequivalence studies are acceptable. Altana's diflorasone diacetate 0.05% ointment is deemed bioequivalent to Psorcon® 0.05% ointment (Pharmacia & Upjohn).

2. All bioequivalence criteria have been met.

E.S. 9/8/98

J. Lee
Division of Bioequivalence
Review Branch II

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9/22/1998

Concur: Dale Conner Date: 10/1/98

Dale Conner, Pharm. D.
Director, Division of Bioequivalence

JLee/jl/ 09-08-98

cc:

Division File